05-16-00

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Express Mail Number: EL 302647881US

TRANSMITTAL FORM

Application Serial Number	08/670,119
Filing Date	June 25, 1996
First Named Inventor	Ng
Group Art Unit	1645
Examiner Name	Hayes, R
Attorney Docket No.	SIM-001

ENCLOSURES *(check all that apply)*

- ☒ Fee Transmittal Form
  - ☒ Check
  - ☒ Copy of Fee Transmittal Form
- ☐ Amendment/Response
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
  - ☐ Letter to Official Draftsperson including Drawings [Total Sheets _____]
- ☐ Extension of Time Request
  Cop of Extension of Time
- ☐ Information Disclosure Statement
  ☐ Form PTO-1449
  ☐ Copies of IDS Citations
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Copy of Notice to File Missing Parts of Application (PTO-1553)
- ☐ Formal Drawing(s)
- ☐ Petition Routing Slip (PTO/SB/69) and Accompanying Petition to Convert to a Provisional Application
- ☐ Power of Attorney (Revocation of Prior Powers)
- ☐ Terminal Disclaimer
- ☐ Executed Declaration and Power of Attorney for Utility or Design Patent Application
- ☐ Small Entity Statement
- ☐ Request for Refund
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Patent Appeals and Interferences
- ☒ Appeal Communication to Group (*Appeal Brief – original and 2 copies)*)
- ☐ Status Letter
- ☒ Return Receipt Postcard
- ☐ Certificate of First Class Mailing under 37 C.F.R. 1.8
- ☐ Additional Enclosure(s) *(please identify below)*

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Express Mail No: EL302647881US

FEE TRANSMITTAL

Note: Effective January 10, 2000.
Patent fees are subject to annual revision

Complete if Known	
Application Serial Number	08/670,119
Filing Date	June 25, 1996
First Named Inventor	Ng
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METHOD OF PAYMENT

1. ☒ Payment Enclosed:
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2. ☒ The Commissioner is hereby authorized to credit or charge any fee indicated below to Deposit Account No. 20-0531.
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FEE CALCULATION

1. FILING FEE

Large Entity Fee ($)	Fee Description	Fee Paid
690	Utility filing fee	
310	Design filing fee	
150	Provisional filing fee	

	Number Filed	Number Extra	Rate	Amount
Total Claims		- 20 =	x $ 18.00 =	
Independent Claims		- 3 =	x $ 78.00 =	
☐ Multiple Dependent Claim(s), if any			$260.00 =	

TOTAL:
SMALL ENTITY DISCOUNT:
SUBTOTAL (1) ($) .00

2. AMENDMENT CLAIM FEES

	Claims Remaining After Amend.	Highest No. Previously Paid For	Present Extra	Rate	Fee Paid
Total	-	=		x $ 18.00 =	
Indep.	-	=		x $ 78.00 =	
☐ First Presentation of Multiple Dep. Claim				+ $260.00 =	

TOTAL: ($)
SMALL ENTITY DISCOUNT: ($)
SUBTOTAL (2) ($).00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee ($)	Small Entity Fee ($)	Fee Description	Fee Paid
130	65	Surcharge - late filing fee or oath	
50	25	Surcharge - late provisional filing fee or	
130	130	Non-English specification	
2,520	2,520	For filing a request for reexamination	
110	55	Extension for reply within first month	
380	190	Extension for reply within second month	
870	435	Extension for reply within third month	
1,360	680	Extension for reply within fourth month	
1,850	925	Extension for reply within fifth month	
300	150	Notice of Appeal	
300	150	Filing a brief in support of an appeal	150.00
260	130	Request for oral hearing	
130	130	Petitions to the Commissioner	
50	50	Petitions related to provisional applications	
240	240	Submission of Information Disclosure Statement (37 CFR 1.97(c))	
130	130	Submission of Information Disclosure Statement (37 CFR 1.97(d))	
690	345	Filing a submission after final rejection (37 CFR 1.129(a))	
690	345	For each additional invention to be examined (37 CFR 1.129(b))	
		Other (Specify)	

SUBTOTAL (3) ($) 150.00

SUBTOTAL (1) .00
SUBTOTAL (2) .00
SUBTOTAL (3) 150.00

TOTAL ($) 150.00

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PATENT
Atty. Docket No. SIM-001
(7434/2)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Ng et al.

SERIAL NO.: 08/670,119 GROUP NO.: 1645

FILING DATE: June 25, 1996 EXAMINER: Hayes, R.

TITLE: RECEPTOR AND TRANSPORTER ANTAGONISTS

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231
Attention: Art Unit 1645
Patricia A. Duffy, Primary Examiner

Sir:

APPLICANTS' BRIEF ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

This is Applicants' Brief in support of an appeal to the Board of Patent Appeals and Interferences from the final rejection of claims 18, 20-37 and 60-65 in the above-referenced application.

REAL PARTIES IN INTEREST

The Real Parties in Interest are the individual inventors, Gordon Y. K. Ng, Philip Seeman, Susan R. George and Brian F. O'Dowd.

RELATED APPEALS AND INTERFERENCES

The Appellants' undersigned legal representative is unaware of another appeal or ~~interference which will directly affect, or be directly affected by,~~ or have a bearing on the Board's decision in this pending appeal.

STATUS OF CLAIMS

Claims 18, 20-37 and 60-65 are pending in the above-identified application, as set out in the attached Appendix, and are the subject of this appeal.

STATUS OF AMENDMENTS

No amendments were filed subsequent to the Final Office Action mailed December 14, 1999. All previous amendments are believed to have been entered.

SUMMARY OF THE INVENTION

The invention, as set forth in the specification and pending claims 18, 20-37 and 60-65 (see Appendix), is directed to the treatment of disorders for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated. The method comprises administering to the subject having the disorder an effective amount of an antagonist peptide consisting essentially of at least four consecutive amino acid residues from the amino acid sequence of said at least one transmembrane domain or a conservative amino acid substitution variant of that peptide to specifically inhibit the activity of the integral membrane protein.

As taught in the specification, many cell receptors or signal transducers are integral membrane proteins. Receptors are the primary targets and mediators of the action of various hormones and drugs. For example, cell surface receptors such as the G protein-coupled receptors, ion channel receptors and tyrosine kinase receptors are integral membrane proteins which span the cell membrane in which they are embedded one or more times. An integral membrane protein such as the tyrosine kinase receptor has a single transmembrane domain, whereas the G protein-coupled receptors have seven transmembrane domains.

The present inventors have shown that a peptide which has the amino acid sequence of a transmembrane domain of an integral membrane protein, or of a portion of that domain, has a specific and selective antagonistic effect on the activity or function of the integral membrane protein from which it is derived. The effectiveness of such antagonists has been demonstrated both *in vivo* and *in vitro* and with respect to a number of different integral membrane proteins. The invention therefore provides a method of specifically inhibiting the activity of an integral membrane protein by selecting as an inhibitor a peptide corresponding to a transmembrane domain amino acid sequence of the integral membrane protein or a fragment thereof. The selectivity of such antagonists has been demonstrated by the inventors. For example, as described in the specification, a peptide corresponding to a portion of one transmembrane domain of the D2 dopamine receptor was shown to cause disassociation of the D2 dopamine receptor but did not cause disassociation of the closely related D1 receptor or the serotonin 5HT1B receptor. This demonstrated selectivity of the antagonist peptides of the invention surpasses the selectivity of agents presently available, for example for blocking D2 receptor activity.

The invention provides a means of selecting an inhibitory antagonist peptide for any integral membrane protein, whether or not that integral membrane protein was previously known, once the amino acid sequence of its transmembrane domain or domains is determined.

The application also describes the importance of integral membrane proteins in various disorders and teaches, for example, that disorders associated with over-activity of a specific receptor, such as schizophrenia which is associated with over-activity of the D2 dopamine receptor, may now be treated with pharmaceuticals of great specificity comprising the antagonist peptides of the invention, based on the transmembrane domain sequence of the D2 dopamine receptor.

FINAL REJECTIONS

A. The Examiner rejected claims 18, 20-37 and 60-65 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make use of the invention.

B. The Examiner rejected claims 18, 20-37 and 60-65 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention, on the grounds that the phrase "when administration of an antagonist . . . is indicated" is unclear.

Claims 18 and 36 were also rejected as indefinite on the grounds that the phrase "consisting essentially of . . . amino acid residues" renders these claims unclear.

C. The Examiner rejected claims 18, 20-22, 36 and 60-61 under 35 U.S.C. 102(b) as anticipated by Lofts et al. (1993), Oncogene 8:2813-2820.

D. The Examiner rejected claims 18, 20-24, 29, 36-37 and 60-61 under 35 U.S.C. 102(e) as anticipated by Murphy et al., U.S. Pat. No. 5,508,384.

ISSUES

1. The first issue presented for appeal is whether the appealed claims 18, 20-37 and 60-65, directed towards methods for treating a disorder for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated, are unpatentable under 35 U.S.C. 112, first paragraph, for failing to describe the invention in such a way as to enable one skilled in the art to make use of the invention.

2. The second issue presented for appeal is whether the appealed claims 18, 20-37 and 60-65, directed towards methods for treating a disorder for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is

indicated, are unpatentable under 35 U.S.C. 112, second paragraph, for failing to define the invention properly.

3. The third issue presented for appeal is whether the appealed claims 18, 20-22, 36 and 60-61, directed towards methods for treating a disorder for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated, are unpatentable under 35 U.S.C. 102(b) over Lofts et al. (1993), Oncogene 8:2813-2820.

4. The fourth issue presented for appeal is whether the appealed claims 18, 20-24, 29, 36-37 and 60-61, directed towards methods for treating a disorder for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated, are unpatentable under 35 U.S.C. 102(e) over Murphy et al., U.S. Pat. No. 5,508,384.

5. Although Applicants believe that the above-identified four issues correspond to all of the pending rejections, Applicants also appeal any other basis for rejection of the pending claims which were not explicitly stated in the Final Office Action but which may be regarded as still pending.

GROUPING OF CLAIMS

The rejected claims 18, 20-37 and 60-65 do not stand or fall together. The group of claims presented in Issue 3 (claims 18, 20-22, 36 and 60-61) is a subset of the group of claims presented in Issues 1 and 2 (claims 18, 20-37 and 60-65) and the group of claims presented in Issue 4 (18, 20-24, 29, 36-67 and 60-61) is a subset of the group of claims presented in Issues 1 and 2. Therefore at least these groups of claims do not stand or fall together. Furthermore, the reasons that each of the individual claims is separately patentable are set forth in the following argument.

ARGUMENT

1. The claimed invention is not unpatentable under 35 U.S.C. 112, first paragraph

The Examiner argued that each claim must recite which specific receptor is to be affected for which specific disorder, in order for the skilled artisan to know how to make and use the instant invention. It is respectfully submitted that this is incorrect. The ordinary skilled artisan will understand, having read the specification, that once he or she is faced with a disorder in which, for example, one wishes to inhibit the activity of a particular integral membrane protein of known amino acid sequence, one can then fashion a very specific antagonist peptide to control activity of that integral membrane protein by following the teachings of the specification to select a suitable antagonist peptide. It is not necessary for the Applicants to teach every possible disorder in which there is a need for inhibition of an integral membrane protein. It is sufficient that the inventors have taught that when one of skill in the art is faced with such a situation, that

person now has a tool at their disposal to treat that disorder by inhibiting the activity of the integral membrane protein by following the teachings of the subject application.

The Examiner further asserted that "only structurally defined molecules can be 'antagonists' for structurally defined receptors and that defining antagonists by 'particular functional characteristics' is not sufficient". However, the antagonist peptides of the invention are structurally defined molecules. They are peptides consisting essentially of at least four consecutive amino acid residues from the amino acid sequence of at least one transmembrane domain of the integral membrane protein whose activity one wishes to inhibit, or conservative amino acid substitution variants of such peptides.

The Examiner argued that claims such as claims 25-27, 30-31 and 33-34 do not recite all defined components and what specifically is to be treated, in order for the skilled artisan to know how to make and use the invention without undue experimentation.

Applicants note, however, that claims 25-27 (D1 dopamine receptor), 30-31 (β1-adrenergic receptor) and 33-34 (α1A-adrenergic receptor), as well as the claims which are dependent on these claims, do clearly specify a receptor whose activity is to be inhibited and do clearly describe the peptides to be used as inhibitors in structural terms. There is no undue experimentation required for one of ordinary skill in the art to utilize the peptides described in the claims to inhibit the activity of the specified receptor in any disorder in which it is desirable to inhibit activity of that receptor. Applicants therefore respectfully submit, that, at least with respect to these claims, the subject matter is fully enabled and the rejection should be withdrawn.

Furthermore, the specification discloses examples relating to many different integral membrane proteins (e.g., G protein coupled receptors such as dopamine receptors and adrenergic receptors). The various examples of inhibition of various integral membrane proteins throughout the specification provide support for the broader claims such as claim 18. Applicants respectfully submit that the determination of whether "administration of an antagonist of an integral membrane protein . . . is indicated" is beyond the scope of the claimed invention and, therefore, need not be described or enabled by the present specification. The prior art, as described in the specification, already includes numerous examples of disorders for which administration of such an antagonist is indicated. And the medical sciences will undoubtedly identify more disorders and more integral membrane proteins for which administration of such an antagonist is indicated. However, for any such indications, the present disclosure describes and enables new methods of treatment based on peptides derived from the transmembrane domains of the relevant integral membrane proteins. Therefore, it is respectfully submitted that the rejections under 35 U.S.C § 112, first paragraph, are improper and should be withdrawn.

For example, the Examiner has repeatedly asserted that EGF receptors are not representative of all neoplastic growth in cancer because all neoplasms are not caused by disjunction of the EGF receptor, and all neoplasms are not necessarily due to disjunction of any other given receptor. The claims, however, are directed to treating a disorder in which inhibition of the activity of an integral membrane protein is indicated. The claims are not directed to

treating disorders, including neoplastic growths, in which there is no indication that inhibition of a particular integral membrane protein is desirable.

In addition, the Examiner asserted that the skilled artisan cannot practice the invention as claimed without undue experimentation "to define what antagonists are specific for what G protein receptors". It is respectfully submitted that this is incorrect. The specification teaches precisely what antagonists are expected to be specific for a particular receptor or integral membrane protein, namely an antagonist peptide consisting essentially of at least four consecutive amino acid residues from the amino acid sequence of at least one transmembrane domain of the integral membrane protein or a conservative amino acid substitution variant thereof.

The Examiner also objected that the specification provides contradictory evidence (in the context of GABA receptors) as to how to determine how and when to successfully practice the invention, arguing that "random administration of random peptides" consisting essentially of at least four consecutive amino acid residues from the transmembrane domain of the relevant integral membrane protein does not reasonably enable the invention. The specification does not teach "random administration of random peptides". It teaches administration of a specifically defined peptide, related in a specifically defined manner to an integral membrane protein when one needs to treat a disorder for which administration of an antagonist of that protein is indicated.

Finally, the Examiner objected that the claims fail to recite using any specific peptide to specifically "inhibit dopamine and/or monoamine transporters" that affect any measurable cell type, disease state or measurable phenotype. The specification teaches, at pages 28-29, that the dopamine transporter and other monoamine transporters are the target of major classes of antidepressant and psychostimulant drugs and that the dopamine transporter is also targeted by drugs of abuse such as cocaine and amphetamines. One of ordinary skill in the art therefore already understands the role of these transporters in a number of disorders. As taught by the specification, the antagonist peptides of the invention, based on the transmembrane domain amino acid sequence of the dopamine transporter or other transporters, provide new specific therapeutic agents useful in these transporter-related disorders as antidepressants and for the relief of drug craving and dependence.

Therefore, for all of the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. §112, first paragraph, should be withdrawn.

2. The claimed invention is not unpatentable under 35 U.S.C. §112, second paragraph

Claims 18, 20-37 and 60-65 have been rejected under 35 U.S.C. §112, second paragraph, on the grounds that it remains unclear when "administration of an antagonist . . . is indicated".

The meaning of the phrase "is indicated" has been discussed briefly above, in dealing with the first issue on appeal. Furthermore, Applicants respectfully submit that the phrase is not

indefinite and that its ubiquitous usage in medical literature demonstrates that one of ordinary skill in the art will readily understand its meaning. Therefore, Applicants respectfully submit that the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

The Examiner also objected to claims 18 and 36 as indefinite for inclusion of the phrase "consisting essentially of . . . amino acid residues". Applicants respectfully traverse the Examiner's position that "at least four consecutive amino acid residues" cannot "consist essentially of" by definition and still be a "conservative amino acid substitution variant of said peptide". The peptide sequence of the claims is any sequence of at least four consecutive amino acids from a transmembrane domain of the relevant integral membrane protein or a conservative amino acid substitution variant of that sequence of at least four consecutive amino acids. A peptide which consists in essence of four consecutive residues from such a transmembrane domain, but which includes additional residues at the N- and/or C- terminus which do not alter the essential function of the peptide in the context of the invention would fall within the scope of the definition. Furthermore, a peptide which consists in essence of such a peptide in which conservative amino acid substitutions have been made would fall within the scope of the definition.

Therefore, for all of the foregoing reasons, Applicants respectfully submit that the rejections under 35 U.S.C. §112, second paragraph, should be withdrawn.

3. The claimed invention is not unpatentable under 35 U.S.C. §102 (b) over Lofts et al.

Claims 18, 20-22, 36 and 60-61 were rejected under 35 U.S.C. §102(b) as being anticipated by Lofts et al. (1993), Oncogene 8:2813-2820.

The Examiner argued that Lofts et al. teaches treatment of *neu* mice with an effective amount of encoded W T peptide sequences which "consist essentially of" at least one transmembrane domain of the mammalian *neu*/EGF integral plasma membrane protein, such that growth of solid tumors in these mice was reduced.

Lofts et al. studied the effect of causing *neu*-transformed cancer cells to express within themselves portions of the *neu* oncogene. The experiment was conducted both *in vitro* and *in vivo*. The growth of these transformed cells was studied in *neu* mice, allowing the affect of *neu* oncogene expression within the tumor cells on tumor cell growth to be observed.

It is clear from a reading of the entire reference that the authors believed it was important to include not only the transmembrane domain of the relevant integral membrane protein but also portions of the specific extracellular and intracellular sequences of that protein. The authors of the paper clearly taught that these extracellular and intracellular portions specific for the integral membrane protein in question were important, in that "the short extracellular and intracellular sequences would anchor the transmembrane portion in the correct orientation". They clearly taught that in order to interfere with the function of the integral membrane protein, transmembrane sequences had to be expressed within a cell and inserted into that cell's

membrane in the correct orientation, guided by the extracellular and intracellular sequences of that protein, under the normal intracellular process for insertion of proteins into the cell membrane.

Lofts et al. did not conceive of using peptides consisting essentially of the amino acid sequence of the transmembrane domain only, or of fragments of that domain, nor did they conceive of administering any portion of an integral membrane protein as a drug. It is respectfully submitted that additional residues at the N- and/or C- terminus of the antagonist peptides of the invention, which residues do not alter the essential function of the peptide, as contemplated in the definition "consisting essentially of", do not render the claims anticipated by Lofts et al. because the peptides of Lofts et al. do not consist essentially of transmembrane sequences.

Therefore, for all of the foregoing reasons, Applicants respectfully submit that the rejection under 35 U.S.C. §102(b) should be withdrawn.

4. Claims 18, 20-24, 29, 36-37 and 60-61are not unpatentable under 35 U.S.C. §102(e) over Murphy et al.

Claims 18, 20-24, 29, 36-37 and 60-61 have been rejected under 35 U.S.C. §102(e) as anticipated by Murphy et al., U.S. Pat. No. 5,508,384.

The Examiner stated that Murphy et al. teaches the use of dopaminergic and adrenergic G protein-coupled transmembrane receptor peptides in pharmaceutical compositions to "treat or prevent" G protein-related diseases.

However, the Examiner relied on only selected portions of the Murphy et al. disclosure to support this rejection, while ignoring other portions of the disclosure which teach in opposite directions and do not support the rejection.

The teachings of Murphy et al. must be considered as a whole, and as one skilled in the art would understand it, having read and absorbed the whole of the teachings. See, for example, In re Wesslau, 147 USPQ 391, 393 (CCPA 1965), where it was held that it is impermissible to pick and choose from a reference "only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art" (emphasis added).

It is respectfully submitted that, having reviewed all of the teachings of Murphy et al., one skilled in the art would not have appreciated the specificity of inhibition of the activity of an integral membrane protein achieved by administration of an antagonist peptide consisting essentially of at least four consecutive amino acid residues selected from the amino acid sequence of a transmembrane domain of that integral membrane protein, as disclosed and claimed in the present application.

Specifically, Murphy et al. proposes that peptides corresponding to portions of the amino acid sequence of G-protein-coupled receptors (GPRs), or peptides somewhat resembling such portions, will mimic the receptors and bind to ligands of the receptors (see, for example, column 6, lines 43-46). Murphy et al. proposes that these peptides will "modulate the binding of GPR ligands to GPRs, such as inhibition or enhancement of binding" (column 8, lines 35-58, emphasis added). Murphy et al. offers no guidance as to how to select peptides for either inhibition or enhancement of binding, and certainly does not teach that peptides derived from a trans-membrane domain of an integral membrane protein will act as antagonists of that protein.

Further, although Murphy et al. proposes as an object of the invention that GPR peptides can be used as potential modulators of G protein-coupled receptor function, Murphy et al. shows absolutely no evidence of any effect of the described peptides on the function of any G protein-coupled receptor. In fact, Murphy et al. shows no data at all involving any G protein-coupled receptor. Therefore, Murphy et al. does not disclose specific inhibition of any G protein coupled receptor activity, and certainly does not teach that peptides derived from a transmembrane domain of an integral membrane protein will act as antagonists of that protein.

The single example in Murphy et al. (columns 37-39) describes the binding of a peptide derived from the dopamine D2 receptor to radioactively labeled spiperone, a ligand of the dopamine D2 receptor. The preparation did not contain any D2 receptors, and neither receptor binding nor receptor function was examined. There is, therefore, no demonstration of any effect of the tested peptide on receptor function, and it cannot be concluded from this experiment that the tested peptide would have affected ligand binding or receptor function in any way. Therefore, Murphy et al. does not teach or disclose specific inhibition of dopamine D2 receptor activity, and certainly does not teach that peptides derived from a transmembrane domain of an integral membrane protein will act as antagonists of that protein.

In contrast, the present inventors have shown that antagonism of an integral membrane protein receptor is highly specific to transmembrane peptides of that receptor. At pages 37-38 of the present specification, an experiment is described in which it was shown that the human dopamine D2 receptor is disrupted by a D2-TM VII peptide (page 37, lines 10-15), whereas the dopamine D1 receptor was unaffected by this D2-TM VII peptide (page 38, lines 2-5). The dopamine D2 receptor was also unaffected by a transmembrane peptide from the α-adrenergic receptor.

Furthermore, the present inventors have shown that a dopamine D2 receptor transmembrane peptide acted *in vivo* in rats as a dopamine D2 receptor antagonist (see, particularly, page 40, lines 13-15), whereas a transmembrane domain peptide derived from the β-adrenergic receptor had no antagonist activity (see Figure 3, panels A and C).

It is clear from reading Murphy et al. as a whole, and considering the range of peptides which are proposed for use, that Murphy et al. failed to conceive of the specificity of receptor antagonism achieved by use of a transmembrane domain peptide of the receptor itself, but not of related receptors, as disclosed in the present application. Indeed, Murphy et al. does not even

teach or disclose whether such peptides would be expected to cause inhibition or enhancement of receptor activity.

For example, Murphy et al. suggests using peptides which comprise an algorithmically-devised "consensus sequence" reflecting the various transmembrane domains of different receptors within a group of related receptors (e.g. Figure 5 shows a consensus peptide reflecting a mixture of the transmembrane sequence of the dopamine D1 and D2 receptors). Murphy et al. even suggests, at column 17, preparing consensus polypeptides across several, perhaps as many as 500, G-protein receptors. In contrast, if one cannot produce specific antagonism of the dopamine D2 receptor by use of the transmembrane domain of a dopamine D1 receptor, as discovered and taught by the present inventors, one certainly would not expect to be able to produce specific antagonism of any particular receptor by using a blended amino acid sequence across 500 different receptors.

In contrast, the present inventors have shown quite clearly that the specific antagonistic effect on receptor function of the present invention is obtained using transmembrane domain peptides and cannot be achieved using peptides from other portions of the receptor molecule. For example, in the experiment described at pages 37-38 of the present application, it was shown that the human dopamine D2 receptor was disrupted by a D2-TM VII peptide but was unaffected by two peptides from cytoplasmic domains of the D2 receptor.

Therefore, taking the teachings of the Murphy et al. reference as a whole, one skilled in the art might conclude that any segment of any GPR protein, or any consensus sequence representing a blending of anywhere from 2 to 500 different G-protein receptors, can be used to modulate ligand binding to a receptor by any described peptide, but without any particular expectation of what effect such a peptide might have on receptor function (i.e., inhibition or enhancement). This is quite different from the teachings of the present disclosure.

For anticipation under 35 U.S.C. 102, a reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present. MPEP 706.02. A rejection based on 35 U.S.C. 102(b) can be overcome by persuasively arguing that the claims are patentably distinguishable from the prior art, or by amending the claims to patentably distinguish over the prior art. MPEP 706.02(b).

The presently claimed invention includes a method of treating a disorder for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated, comprising administering an effective amount of an antagonist peptide consisting essentially of at least four consecutive amino acid residues from the amino acid sequence of a transmembrane domain of the protein to specifically inhibit the activity of the integral membrane protein. Murphy et al. does not teach this method. In particular, Murphy et al. does not teach that peptides consisting essentially of sequences derived from a transmembrane domain of an integral membrane protein will act as antagonists of that protein and may be used to specifically inhibit the activity of the protein from which they are derived.

Therefore, for all of the foregoing reasons, Applicants respectfully submit that the rejections under 35 U.S.C. §102(e) should be withdrawn.

CONCLUSION

Applicants believe that the foregoing arguments are responsive to all of the outstanding rejections of the pending claims. Applicants assume that any previous rejections not repeated in the Final Office Action have been overcome by the Applicants' previous arguments. If the Examiner considers that any of these prior rejections remain pending, Applicants request that any such rejections be raised in the Examiner's answer to provide the Applicants with an opportunity to respond.

It is respectfully submitted that the foregoing arguments overcome all of the pending rejections of the Final Office Action. Therefore, the Commissioner is requested to reverse the Final Rejections and to permit the application to proceed to allowance.

A petition and fee for the filing of this Brief on Appeal is submitted herewith.

Respectfully submitted,

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APPENDIX

Claims on Appeal - U.S. Ser. No. 08/670,119

18. A method of treating, in a mammal, a disorder for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated, said method comprising administering to the mammal an effective amount of an antagonist peptide consisting essentially of at least four consecutive amino acid residues from the amino acid sequence of said at least one transmembrane domain or a conservative amino acid substitution variant of said peptide to specifically inhibit the activity of the integral membrane protein.

20. The method of claim 18 wherein the integral membrane protein is an intracellular membrane.

21. The method of claim 18 wherein the integral membrane protein is a plasma membrane protein.

22. The method of claim 21 wherein the integral membrane protein is selected from the group consisting of

(a) a G-protein coupled receptor;
(b) a tyrosine kinase receptor;
(c) a channel protein;
(d) a T cell antigen receptor; and
(e) a transporter protein.

23. The method of claim 22 wherein the integral membrane protein is a G-protein coupled receptor.

24. The method of claim 23 wherein the G-protein coupled receptor is a dopamine receptor.

25. The method of claim 24 wherein the dopamine receptor is the D1 dopamine receptor and the peptide is selected from the group consisting of

(a) ILTACFLSLLILSTLLGNTLVCAAV (SEQ. ID NO: 9);

(b) FFVISLAVSDLLVAVLVMPWKAVAEIA (SEQ. ID NO: 10);

(c) NIWVAFDIMCSTASILNLCVISVD (SEQ. ID NO: 11);

(d) AAFILISVAWTLSVLISFIPVQLSW (SEQ. ID NO: 12);

(e) TYAISSSVISFYIPVAIMIVTYTRI (SEQ. ID NO: 13);

(f) TLSVIMGVFVCCWLPFFILNCILPFC (SEQ. ID NO: 14);

(g) FDVFVWFGWANSSLNPIIYAFNAD (SEQ. ID NO: 15); and

(h) an effective analogue or fragment of (a) to (g).

26. The method of claim 24 wherein the dopamine receptor is a D2 dopamine receptor and the peptide is selected from the group consisting of

(a) ATLLTLLIAVIVFGNVLVCMAVS (SEQ. ID NO: 1);

(b) LIVSLAVADLLVATLMPWVVYLEVV (SEQ. ID NO: 2);

(c) IVFTLDVMMCTASILNLCAISI (SEQ. ID NO: 3);

(d) VTVMISIVWVLSFTISCPLLFGL (SEQ. ID NO: 4);

(e) PAFVVYSSIVSFYVPFIVTLLVYI (SEQ. ID NO: 5);

(f) MLAIVLGVFIICWLPFFITHILN (SEQ. ID NO: 6);

(g) VLYSAFTWLGYVNSAVNPIIYTTF (SEQ. ID NO: 7); and

(h) an effective analogue or fragment of (a) to (g).

27. The method of claim 24 wherein the dopamine receptor is a D2 dopamine receptor and the peptide is selected from the group consisting of

~~(a) YATLLTLLIAVIVFGNVLVC (SEQ. ID NO: 61);~~

(b) VSLAVADLLVATLVMPWVVY (SEQ. ID NO: 60);

(c) TLDVMMCTASILNLCAISID (SEQ. ID NO: 59);

(d) RVTVMISIVWVLSFTISCPL (SEQ. ID NO: 58);

(e) PAFVVYSSIVSFYVPFIVTL (SEQ. ID NO: 57);

(f) LAIVLGVFIICWLPFFITHI (SEQ. ID NO: 56); and

(g) LYSAFTWLGYVNSAVNPIIY (SEQ. ID NO: 55).

28. The method of claim 26 wherein the disorder is selected from the group consisting of schizophrenia, Huntington's disease, Tourette's syndrome and substance abuse.

29. The method of claim 23 wherein the G-protein coupled receptor is an adrenergic receptor.

30. The method of claim 29 wherein the adrenergic receptor is a β1-adrenergic receptor and the peptide is selected from the group consisting of

(a) GMGLLMALIVLLIVAGNVLVIVAI (SEQ. ID NO: 16);

(b) IMSLASADLVMGLLVVPFGATIVV (SEQ. ID NO: 17);

(c) ELWTSVDVLCVTASIETLCFIALD (SEQ. ID NO: 18);

(d) RGLVCTVWAISALVSFLPILMHWW (SEQ. ID NO: 19);

(e) RAYAIASSVVSFYVPLCIMAFVYL (SEQ. ID NO: 20);

(f) LGIIMGVFTLCWLPFFLANVVKAF SEQ. ID NO: 21);

(g) RLFVFFNWLGYANSAFNPIIYCRS (SEQ. ID NO: 22); and

(h) an effective analogue or fragment of (a) to (g).

31. The method of claim 29 wherein the receptor is a β1-adrenergic receptor and the peptide is FFNWLGYANSAFNP (SEQ. ID NO: 30).

32. The method of claim 30 wherein the disorder is cardiac arrhythmia.

33. The method of claim 29 wherein the adrenergic receptor is an α1A-adrenergic receptor and the peptide is selected from the group consisting of

(a) GVGVGFLAAFILMAVAGNLLVILSV (SEQ. ID NO: 23);

(b) FIVNLAVADLLLSATVLPFSATMEVL SEQ. ID NO: 24);

(c) DVWAAVDVLCCTASILSLCTISV (SEQ. ID NO: 25);

(d) AAILALLWVVALVVSVGPLLGWKEP (SEQ. ID NO: 26);

(e) AGYAVFSSVCSFYLPMAVIVVMYC (SEQ. ID NO: 27);

(f) LAIVVGVFVLCWFPFFFVLPLGSL (SEQ. ID NO: 28);

(g) EGVFKVIFWLGYFNSCVNPLIYPCS (SEQ. ID NO: 29); and

(h) an effective analogue or fragment of (a) to (g).

34. The method of claim 29 wherein the receptor is an α1A-adrenergic receptor and the peptide is VFKVIFWLGYFNSCVN (SEQ. ID NO: 31).

35. The method of claim 33 wherein the disorder is hypertension.

36. The method of claim 18 wherein the integral membrane protein has a plurality of transmembrane domains and wherein the antagonist peptide consists essentially of at least four consecutive amino acid residues from the amino acid sequence of any one of said plurality of transmembrane domains or a conservative amino acid substitution variant of said peptide.

37. The method of claim 18 wherein the integral membrane protein is a human protein.

60. The method of claim 22 wherein the integral membrane protein is a tyrosine kinase receptor.

61. The method of claim 60 wherein the tyrosine kinase receptor is an epidermal growth factor receptor.

62. The method of claim 22 wherein the integral membrane protein is a channel protein.

63. The method of claim 22 wherein the integral membrane protein is a T cell antigen receptor.

64. The method of claim 22 wherein the integral membrane protein is a transporter protein.

65. The method of claim 64 wherein the transporter protein is a dopamine transporter.